in a G-1b replicon.[35–38] Numerous combinations of bridging and elongation strategies that have resulted in tri- and tetracyclic scaffolds claiming to possess potent G-1b inhibitory activity have also been reported (see **28**).[39] Scaffolds with increased flexibility (see **27**) suffered a loss in inhibitory activity.[40]

Another strategy explored the utility of benzimidazole and its aza variants as bioisosteric replacements for the aryl imidazole moiety (Figure 1.8). Here again, analogs with a wide range of core lengths have exhibited G-1b EC_{50}s of <1 nM.[33,41–43] Although detailed data are not available to make a comparative assessment regarding inhibitory activity towards other genotypes, it is noteworthy that **33b** was reported to exhibit G-1a and G-1b inhibitory potencies of 50 and 3 pM, respectively, along with 23% oral bioavailability in monkeys when administered as a dihydrochloride salt.[44]

Numerous hybrid scaffolds have been explored that lie outside the bis-imidazole or bis-benzimidazole scaffolds (see Figure 1.9). The most common structural elements include combinations of imidazole and benzimidazole moieties, as in **34**, or cases where one of these two moieties is hybridized with other potential bioisosteres, including a primary amide (**35**), a thienoimidazole (**36**) or a quinazolinone (**37**).[45–48]

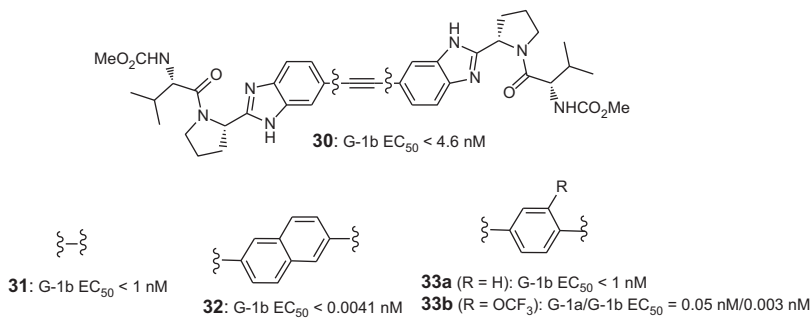

Figure 1.8 Bis-benzimidazole core analogs.

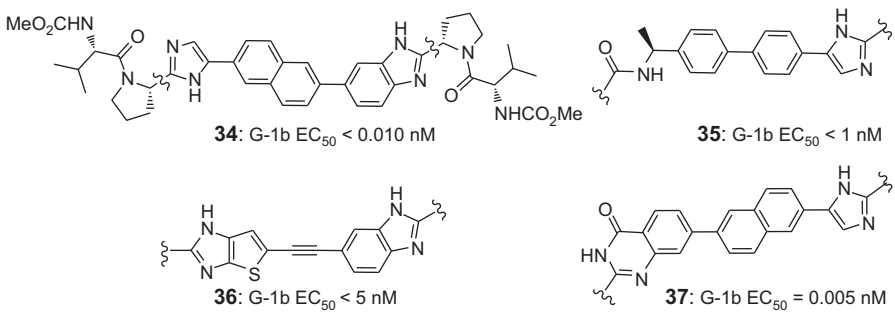

Figure 1.9 Hybrid core analogs.